REMARKS

Summary of the Invention

The present invention features a method for determining the prognosis of a patient diagnosed with Alzheimer's disease, neurofibromatosis, Huntington's disease, depression, amyotrophic lateral sclerosis, multiple sclerosis, stroke, Parkinson's disease, multiple infarcts dementia, a prion disease, a pathology of the developing nervous system, a pathology of the aging nervous system, an infection of the nervous system, a dietary deficiency, or a cardiovascular injury. The method is performed by determining the patient's *apoE* allele load, where the presence of an *apoE4* allele or ApoE4 protein isoform is indicative of a poor patient outcome.

Summary of the Office Action

Claims 1, 3-15, and 17-20 are pending. Claims 17-20 have been withdrawn. Claims 1 and 3-15 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 1, 3, 4, and 12 are rejected under 35 U.S.C. § 102 (a) for anticipation by Roberts *et al.* (WO96/03656; hereinafter "Roberts") and claim 11 is rejected under 35 U.S.C. § 103(a) for obviousness over Roberts. Claims 1, 3, 4, 11, 12, and 15 are rejected under 35 U.S.C. § 103(a) for being unpatentable over Morris *et al.* (J. Neural Transm., 47:205-218, 1996; hereinafter "Morris") in view of Poirier *et al.* (Proc. Natl. Acad. Sci. USA, 92:12260-12264, 1995; hereinafter "Poirier"). Claims 1 and 3-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,935,781 (hereinafter "the '781 patent"). These claims are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

claims 1-14 of co-pending application, U.S. Serial No. 09/865,753 (hereinafter "the '753 application"). By this reply, Applicant cancels claims 4, 9, and 15, amends claims 1, 5, 6, 10, 11, and 12, and addresses each of the Examiner's objections and rejections below. Applicant respectfully requests reconsideration of the claims.

Support for the amendment

Support for the amendment to claim 1 is found in cancelled claims 4 and 9. The amendment to claims 5, 6, and 10 correct dependency due to the cancellation of claims 4 and 9. The amendment to claims 11 and 12 is for clarification. No new matter is added by the amendment.

Domestic Priority

The Examiner acknowledges Applicant's claim for domestic priority based on U.S. Serial No. 08/727,637 and National Phase Application PCT/CA95/00240, but states that "the claims of the instant application are not fully supported under 35 U.S.C. § 112 by these earlier filed parent applications." (Office Action, p. 1.) Consequently, the Examiner has established the filing date for the present application to be December 26, 1996, based on the filing of the parent application, U.S. Serial No. 08/766,975.

Applicant notes, for the record, that the date of filing of U.S. Serial No. 08/766,975 is, in fact, December 16, 1996. Accordingly, the effective filing date of the present application is December 16, 1996 and not, December 26, 1996, as is indicated by the Examiner on page 1 of the Office Action (see the Filing receipt for U.S. Serial No. 09/500,162; provided herewith).

Based upon the Examiner's conclusion, the priority claims to U.S. Serial No. 08/727,637 and PCT/CA95/00240 are withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1 and 3-15 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner asserts that the present application fails to provide adequate guidance and support for the present scope of the claims, provides no working embodiments, and that practicing the claimed invention would require undue experimentation (Office Action, p. 4-8). Specifically, the Examiner states that the disclosure fails to support any relationship between *apoE* allele load and non-AD neurological disorders, and that this lack of correlation is established in the prior art (Office Action, p. 7-8). The Examiner further argues that the specification fails to adequately delimit the predictive value of *apoE* allele load with responsiveness to therapy (Office Action, p. 6). Applicant has amended the claims, as is discussed below, and believes the rejection can now be withdrawn.

Enablement of an invention, under 35 U.S.C. § 112, first paragraph, "requires a determination of whether the disclosure of the invention, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." (M.P.E.P. § 2164.01.) The test of enablement is whether one skilled in the art, given the information provided in the specification, could make and use the invention without undue experimentation. Applicant has plainly satisfied this standard.

The Presently Claimed Methods Do Not Require Undue Experimentation

The present claims, as amended, are directed to a method for determining the prognosis for a patient diagnosed with Alzheimer's disease, neurofibromatosis, Huntington's disease, depression, amyotrophic lateral sclerosis, multiple sclerosis, stroke, Parkinson's disease, multiple infarcts dementia, a prion disease, a pathology of the developing nervous system, a pathology of the aging nervous system, an infection of the nervous system, a dietary deficiency, or a cardiovascular injury. All are diseases involving the nervous system. The method simply requires determining the *apoE* allele load of a patient already diagnosed with one of the aforementioned diseases. The determination of the presence of an *apoE* ε4 allele or an ApoE4 protein isoform indicates a poor prognosis. This is clearly described in the specification (see, e.g., page 10, lines 20-22, and page 11, line 23, through page 12, line 4).

The invention is premised on the Inventor's discovery that a patient's *apoE* genotype is a determinative factor in the general neuronal health of that patient. In other words, *apoE* allele load is predictive of the general state of neurons in the patient (i.e., the relative health or fragility of neurons). Applicant observed that *apoE4* carriers demonstrated a marked loss of neurons, for example, cholinergic neurons, and a reduction in neuronal choline acetyltransferase (ChAT) activity and choline levels versus *apoE3* carriers (see page 11, lines 17-22, of the specification). Applicant further recognized that this loss of neurons and neuronal activity was directly related to defects in apoE4 protein function and that this defect occurred regardless of the patient's specific neurological disorder. Based on this discovery, Applicant tested and verified the belief that a patient's *apoE* allele load can be used to determine their prognostic outcome, regardless of the specific neurological disease (i.e., the patient can be an AD or a non-AD patient). Furthermore, an understanding of the molecular basis for the neurological disorder is not

required to practice the claimed methods; all that is required is the ability to determine the diagnosed patient's *apoE* status. As a consequence, the presently claimed methods do not require undue experimentation, but rather can be easily performed using well-defined techniques described in, e.g., the specification, and known in the art (see, e.g., page 12, line 18, through page 16, line 21, of the specification).

Post-Filing Art Validates the Methods of Applicant's Invention

The Examiner states that the disclosure fails to support any relationship between *apoE* allele load and non-AD neurological disorders. The Examiner supports this conclusion by citing Morris, Mattila *et al.* (Acta Neuropathol. (Berl.) 96:417-420, 1998; hereinafter "Mattila"), Rubinsztein *et al.* (Mol. Cell Probes 8:519-525, 1994; hereinafter "Rubinsztein"), Salvatore *et al.* (Neuroscience Letters 199:95-98, 1995; hereinafter "Salvatore"), and Marder *et al.* (Neurology 44:1330-1331, 1994; hereinafter "Marder"), which the Examiner states "clearly illustrates that the *apoE* ε4 allele is not responsible for many neurological deficits. Therefore determining the *apoE* allele load would be of no predictive value." (Office Action, p. 8.) The references cited by the Examiner merely describe attempts that were made to uncover a relationship between *apoE* genotype and the ability to diagnose or even forecast the onset of a particular neurological disease. In contrast, the present invention does not utilize a patient's *apoE* status to diagnose or forecast the onset of a particular neurological disease, but rather provides a method for determining the prognosis of a patient already diagnosed with the neurological disorders recited in present claim 1 based on their *apoE* allele load. The references cited by the Examiner are not relevant to this point and, therefore, are not demonstrative of any uncertainty with respect to the present invention.

In addition, Applicant directs the Examiner's attention to the Declaration of Judes Poirier, Ph.D. (hereinafter "the Poirier Declaration"; filed herewith), which describes three exemplary references, Fazekas *et al.* (J. Neurol. Neurosurg. Psychiatry, 69:25-28, 2000; hereinafter "Fazekas"; provided herewith), Leung *et al.* (Stroke, 33:548-552, 2002; hereafter "Leung"; provided herewith), and Drory *et al.* (J. Neurol. Sci., 190:17-20, 2001; hereinafter "Drory"; provided herewith), published after Applicant's discovery, which further support Applicant's contention that the art recognizes the predictive benefit associated with the *apoE* allele load determination method of the present invention (see paragraphs 4-8 of the Poirier Declaration).

Fazekas demonstrates that the *apoE4* genotype is associated with poor prognosis in patients diagnosed with multiple sclerosis; a neurodegenerative disorder recited in present claim 1 (see, e.g., the abstract of Fazekas, and paragraph 5 of the Poirier Declaration).

Leung describes the relationship of aneurismal subarachnoid hemorrhage and the *apoE4* genotype in 72 hospitalized patients over the course of two years and demonstrates that the presence of an *apoE4* genotype correlates with poor patient outcome following aneurysm, regardless of therapeutic treatment (see Leung, page 549, column 2, paragraph 4; see also paragraph 6 of the Poirier Declaration; see, e.g., "stroke" recited in present claim 1).

Drory describes a controlled study with 100 patients diagnosed with amyotrophic lateral sclerosis in which the presence of the *apoE4* allele in these patients is indicative of a poor prognosis with respect to disease progression and survival (Abstact, page 17, of Drory, and paragraph 7 of the Poirier Declaration). Drory further reiterates that carriers of the *apoE4* allele are associated with poor clinical outcomes for other neurodegenerative disorders, including, for example, Alzheimer's Disease, dementia associated with stroke, and multiple sclerosis; all of

which are recited in present claim 1 (see Drory, page 19, column 1, paragraph 1, and column 2, paragraph 2).

In each of the aforementioned clinical studies, the *apoE4* allele load was determined in patients diagnosed with various neuropathologies and a clear correlation was found between the presence of the *apoE4* allele and poor prognosis, consistent with Applicant's teachings.

The Presently Claimed Methods Can be Used to Determine an AD or a Non-AD Patient's Prognosis

The Examiner also states that:

> The claims are excessively broad and encompass an extremely large genus of disparate neurological disorders...all...[having] different pathological determinants...Accordingly, the skilled artisan would not consider it reasonable to assert that the *apo*E allele frequency in all these various disorders...would be predictive of therapeutic responsiveness and clinical outcome. (Office Action, pp. 5-6.)
>
> The disclosure fails to provide any working embodiments involving non-AD neurological disorders. (Office Action, p. 6.)

In response, Applicant directs the Examiner to the M.P.E.P. § 2164.01(b), which states:

> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833,839, 166 USPQ 18, 24 (CCPA 1970).

The specification states that the prognostic outcome of a patient diagnosed with a neurological disorder can be determined by establishing that patient's *apoE* allele load (see, e.g., page 4, line 15, through page 5, line 11, of the specification). Although the examples provided in the specification are directed solely to the use of this method in AD patients, the specification clearly states that "the observation regarding apoE allele load and drug therapies can be

generalized to non-AD neurological diseases because the underlying mechanism altered by the apoE allele load is not AD-specific." (See page 11, line 23, through page 12, line 1, of the specification.) In further support of this belief, Applicant again refers the Examiner to the Poirier Declaration, which provides data demonstrating that the claimed invention can be used, as is described in the specification, to determine the prognosis of a patient diagnosed with a neurological disorder based solely on the *apoE* genotype of that patient.

As is detailed in the Poirier Declaration, the presently claimed methods were additionally evaluated in patients suffering from two non-AD neurological diseases: Parkinson's disease (PD) and multiple sclerosis (MS), both of which are recited in present claim 1. In the first study, the *apoE* genotype of 59 patients with PD was determined and compared to the PD patients' response to treatment (see paragraphs 9 and 10 of the Poirier Declaration). The study concluded that there was a strong negative correlation between a PD patient's response to drug therapy and *apoE4* allele load; PD patients with no *apoE4* allele exhibited a better response to treatment, as measured by an improvement in symptoms of rigidity and tremor, than did those PD patients with an *apoE4* allele (see Table 1, Exhibit A). This study confirmed a direct correlation between the presence of an *apoE4* allele in a patient with PD and their prognostic outcome (i.e., the presence of an *apoE4* allele in a patient with PD is indicative of a poor prognosis).

Applicant also examined the relationship between *apoE* genotype and prognostic outcome in patients with MS (see paragraphs 11 and 12 of the Poirier Declaration). The *apoE* genotype of 65 patients suffering from MS was determined and compared to the MS patients' response to drug treatment. The non-*apoE4* MS patients responded better to drug therapy than did those MS patients that carried an *apoE4* allele. Therefore, the results of this study again

confirmed a correlation between the presence of an *apoE4* allele and a poor prognostic outcome (see Tables 4 and 5, Exhibit D).

For the sake of completeness, it is noted that in a study of the *apoE* genotype of 51 patients suffering from stroke the presence of an *apoE4* allele did not correlate with a poor prognosis for two specific parameters: speed of recovery and rehabilitation time (see paragraph 13 of the Poirier Declaration). Based upon this result and Drory, as discussed above, Applicant suggests that a patient's *apoE4* status correlates with some, but not all aspects of stroke prognosis (i.e., Drory confirmed a correlation between *apoE4* status and poor prognostic outcome in patients suffering from dementia associated with stroke).

In sum, the examples discussed above provide further validation of Applicant's discovery and demonstrate a clear correlation between the *apoE* allele load in patients diagnosed with neurological disorders other than Alzheimer's disease, and their prognostic outcome (see paragraph 14 of the Poirier Declaration). Therefore, the present methods can be used to determine an AD or a non-AD patient's prognosis, as is discussed above. The methods are easy to practice; all that is required is a determination of a patient's *apoE* genotype. Furthermore, based on the specification as filed, the examples described in the Poirier Declaration and as discussed above, and the post-filing references Fazekas, Leung, and Drory, the present claims are not unduly broad, bear a reasonable correlation to the full scope of the claimed invention, and are fully enabled. Accordingly, Applicant respectfully requests that this aspect of the rejection be withdrawn.

Guidance Provided in the Specification: Correlation of apoE Allele Loads with Treatment

The Examiner states that *apoE* ε4 allele load in AD patients is reasonably predictive of patient responsiveness to cholinomimetic therapy, but that "the disclosure fails to provide any

guidance pertaining to other suitable therapeutic compounds and the predictive value of measuring the apoE allele load in these settings." (Office Action, pp. 6.) While Applicant disagrees, the claims have been amended and no longer recite therapeutic efficacy. Thus, this aspect of the rejection may now be withdrawn.

In light of the foregoing remarks and with regard to the Poirier Declaration, Applicant submits that, with respect to all of the issues discussed above in connection with the rejection of claims 1 and 3-15 under 35 U.S.C. § 112, first paragraph, the claimed invention is enabled to its full scope. Dr. Poirier has not only provided an expert opinion as to the successful practice of the presently claimed method, he has also supported that position with clear facts, data, and reasoning. Such evidence and reasoning cannot be dismissed in the absence of compelling evidence to the contrary, and such evidence is not provided in this case. Therefore, in view of the above remarks, Applicant submits that the present specification is more than sufficient to teach those skilled in the art both "how to make" and "how to use" the invention of claims 1 and 3-15 without undue experimentation. Accordingly, the rejection of claims 1 and 3-15 under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn.

Rejection under 35 U.S.C. § 102 (a)

Claims 1, 3, 4, and 12 are rejected under 35 U.S.C. § 102 (a) for anticipation over Roberts. The Examiner states that "Roberts and colleagues disclose a prognostic method for assessing patient outcome in subjects who have sustained head injuries by determining the *apoE* allele load." Applicant has amended claim 1, as is discussed below, and believes this rejection can now be withdrawn.

Claim 1 has been amended to recite that the patient is diagnosed with one of the following conditions: Alzheimer's disease, neurofibromatosis, Huntington's disease, depression,

amyotrophic lateral sclerosis, multiple sclerosis, stroke, Parkinson's disease, multiple infarcts dementia, a prion disease, a pathology of the developing nervous system, a pathology of the aging nervous system, an infection of the nervous system, a dietary deficiency, or a cardiovascular injury. Roberts discloses a prognostic method to assess patient outcome in head injury patients or patients who may be at risk of sustaining a head injury. Roberts fails to teach or suggest a method for creating a prognosis protocol for a patient already diagnosed with any of the conditions recited in claim 1, as presently amended, nor does Roberts contemplate determining a patient's *apoE* allele load for use as an indication of patient outcome in cases other than head injury. Therefore, Roberts fails to teach or suggest all of the limitations of the present claims. Accordingly, the rejection of claims 1, 3, 4, and 12 under 37 C.F.R. § 102(a) may be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claim 11 stands rejected under 35 U.S.C. § 103(a) for obviousness in view of Roberts. The Examiner states that "it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to assess various parameters...such as age, sex, past familial involvement, etc., and to incorporate these parameters into the final prognostic protocol." Applicant respectfully disagrees.

As is discussed above, claim 1, from which claim 11 depends, has been amended to recite that a patient is diagnosed with a specific neurological condition. None of the neurological conditions recited in claim 1 was taught or suggested by Roberts. Because the method of claim 1 is not anticipated or made obvious by the method disclosed by Roberts, claims dependent therefrom are also novel and non-obvious over Roberts (see, e.g., M.P.E.P. § 2143.03).

Accordingly, Applicant respectfully requests that the rejection of claim 11 under 35 U.S.C. § 103(a) for obviousness in view of Roberts be withdrawn.

In addition, claims 1, 3, 4, 11, 12, and 15 are rejected under 35 U.S.C. § 103(a) for obviousness over Morris in view of Poirier. The Examiner states that "Morris and colleagues reported that Lewy body dementia (LBD) patients displayed an increased Apo E ε4 allele frequency...[and that] [t]his teaching includes all of the claimed limitations except those pertaining to the development of a prognostic protocol," which is provided by Poirier (Office Action, p. 3.) Applicant respectfully traverses this rejection.

Applicant directs the Examiner's attention to the Poirier Declaration, which states that Dr. Poirier is the only inventor of the work described in Poirier et al. (1995) and that the other authors worked under Dr. Poirier's direction and control and did not contribute to the claimed inventive concepts (see paragraph 15 of the Poirier Declaration). In addition, as is indicated in the Table of Contents from the Proceedings of the National Academy of Sciences, USA (enclosed herewith as Exhibit F), the Poirier reference was released on December 19, 1995 and was received by the Tufts University Health Sciences Library on December 29, 1995. As is noted above, the date from which the claims of the present application can claim priority is December 16, 1996, based on the filing date of U.S. Serial No. 08/766,975, the parent application of the present application. Therefore, because the publication date is within one year of the Applicant's filing date and is Applicant's own work, the Poirier reference can no longer be considered prior art under 35 U.S.C. § 102 (a) (*In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982)).

Morris alone fails to teach or suggest all of the limitations of the rejected claims, as is acknowledged by the Examiner, therefore, Applicant respectfully submits that the rejection of

claims 1, 3, 4, 11, 12, and 15 under 35 U.S.C. § 103(a) over Morris in view of Poirier should be withdrawn.

Rejection for Non-Statutory Obviousness-Type Double Patenting

Claims 1 and 3-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of the '781 patent. The Office asserts that:

> The claims of the instant application are directed toward prognostic protocol methods involving patients with neurological disorders and apoE allele load determinations while the claims of the '781 patent are directed toward patient prognostic protocols involving patients with cognitive impairments, which is encompassed by neurological disorders. Thus, the claims of the instant application fall within the scope of the claims of the '781 patent and would result in the unjustified or improper timewise extension of the "right to exclude" granted by a patent.

Applicant respectfully traverses this rejection.

Claim 1 of the '781 patent is a method for determining the responsiveness of human subjects with cognitive impairments to a cholinomimetic drug by determining the number of copies of apoE4 gene alleles in the subject. Claim 2 of the '781 patent recites a method for treating human subjects with cognitive impairments by identifying the subjects using the method of claim 1 and administering a cholinomimetic drug to improve cognitive performance. The methods of the '781 patent establish that a subject is predisposed to respond to a cholinomimetic drug if the subject lacks at least one apoE4 gene. The '781 patent also discloses that a patient's apoE4 gene status can be determined indirectly by determining the presence of apoE2 and/or apoE3 gene alleles using apoE2 and apoE3 gene probes, as is disclosed in claim 4.

Present claims 1, 3, 5-8, and 10-14 differ from the claims of the '781 patent by reciting a method of determining the prognosis of a patient having been diagnosed with a specific neurological disease. The patient's *apoE* status indicates the patient's prognosis; the presence of at least one *apoE4* allele indicates a poor prognosis. Based solely on the claims, the '781 patent does not teach or suggest that the prognosis of a patient diagnosed with any one of the diseases or conditions listed above can be established by determining that patient's *apoE4* allele load. Because claims 1-4 of the '781 patent do not teach or suggest all of the limitations of claims 1, 3, 5-8, and 10-14, Applicant respectfully requests that the obviousness-type double patenting rejection over the claims of the '781 patent be withdrawn.

Rejection for Provisional Obviousness-Type Double Patenting

Claims 1 and 3-15 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of co-pending application, U.S. Serial No. 09/865,753. In response to the provisional double patenting rejection, Applicant will submit a terminal disclaimer, if necessary, to overcome the rejection once otherwise allowable subject matter has been determined.

CONCLUSION

Applicant submits that the claims are in condition for allowance, and such action is respectfully requested. If the Office does not concur, a telephonic interview with the undersigned is hereby requested.

Also enclosed is a Petition to extend the period for replying for 3 months, to and including April 30, 2003, and a check for the fee required under 35 U.S.C. § 1.17(a).

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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FOR

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